DEPARTMENT OF HEALTH & HUMAN SERVICES Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 17-386/SLR-032
NDA 19-532/SLR-012

Celltech Pharmaceuticals, Inc.
Attention: R. Andrew Morgan, R.Ph.
755 Jefferson Road
P.O. Box 31710
Rochester, NY 14603-1710

Dear Mr. Morgan:

Please refer to your supplemental new drug applications dated July 17, 2001 submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Zaroxolyn (metolazone) 2 ½, 5, 10 mg Tablets and Mykrox (metolazone) ½ mg Tablets.

These "Special Supplements- Changes Being Effected in 30 days" provide for revised Final Printed Labeling to add and strengthen warnings and adverse actions as follows:

NDA 17-386 (Zaroxolyn)
NDA 19-532 (Mykrox)

1. The phrase "and/or Hypokalemia" has been added to the WARNINGS: Rapid Onset Hyponatremia heading to read:

   "WARNINGS: Rapid Onset Hyponatremia and/or Hypokalemia:"

2. Under WARNINGS: Hypokalemia: the phrase "and appropriate" has been added to the second sentence to read:

   "Serum potassium should be determined at regular and appropriate intervals, and dose reduction…."

NDA 17-386 (Zaroxolyn)

1. Under ADVERSE REACTIONS: Dermatologic/Hypersensitivity: the text "Toxic epidermal necrolysis (TEN), Stevens-Johnson Syndrome," has been added to read:

   "Dermatologic/Hypersensitivity: Toxic epidermal necrolysis (TEN), Stevens-Johnson Syndrome, necrotizing angiitis (cutaneous vasculitis), purpura, dermatitis (photosensitivity), urticaria, and skin rashes."

2. Thrombocytopenia was deleted from the paragraph describing adverse reactions reported with similar antihypertensive-diuretics and added to "ADVERSE REACTIONS: Hematologic:" to read:

   "Hematologic: Aplastic/hypoplastic anemia, agranulocytosis, leukopenia, thrombocytopenia."

3. Dry mouth was deleted from the paragraph describing adverse reactions reported with similar antihypertensive-diuretics and added to "ADVERSE REACTIONS: Other:" to read:

   "Other: Transient blurred vision, chills, dry mouth."

In addition, the labeling has been updated for a change in the company name from "Medeva Pharmaceuticals, Inc." to "Celltech Pharmaceuticals, Inc."

NDA 19-532 (Mykrox)

1. Under ADVERSE REACTIONS: Dermatologic/Hypersensitivity: the text "Toxic epidermal necrolysis (TEN), Stevens-Johnson Syndrome," has been added to read:

   "Dermatologic/Hypersensitivity: Toxic epidermal necrolysis (TEN), Stevens-Johnson Syndrome, necrotizing angiitis (cutaneous vasculitis), purpura, dermatitis, photosensitivity, urticaria."

2. Thrombocytopenia was deleted from the paragraph describing rare adverse experiences reported in association with similar antihypertensive-diuretics and was added to "Other Adverse Experiences: Hematologic:" to read:

   "Hematologic: Aplastic (hypoplastic) anemia, agranulocytosis, leukopenia, thrombocytopenia."

In addition, we note the following minor editorial changes:

1. The labeling has been updated for a change in the company name from "Medeva Pharmaceuticals, Inc." to "Celltech Pharmaceuticals, Inc."

2. The text in the HOW SUPPLIED section was changed from "Store at room temperature. Dispense in a tight, light-resistant container. Keep out of the reach of children" to "Store at 25ºC (77ºF); excursions permitted to 15º-30ºC (59º-86ºF) [See USP Controlled Room Temperature]. Protect from light. Keep out of the reach of children."

3. The statement: "Caution: Federal law prohibits dispensing without prescription." was changed to "R_x Only" and moved to the beginning of the package insert under the drug name.

We have completed the review of these supplemental applications and have concluded that adequate information has been presented to demonstrate that the drug products are safe and effective for use as recommended in the submitted Final Printed Labeling. Accordingly, these supplemental applications are approved effective on the date of this letter.

If a letter communicating important information about this drug product (i.e., a "Dear Health Care Professional" letter) is issued to physicians and others responsible for patient care, we request that you submit a copy of the letter to this NDA and a copy to the following address:

MEDWATCH, HF-2
FDA
5600 Fishers Lane
Rockville, MD 20857

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, please call:

Mr. Daryl Allis
Regulatory Health Project Manager
(301) 594-5309.

Sincerely,

Raymond J. Lipicky, M.D.
Director
Division of Cardio-Renal Drug Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research